REMARKS

Claim Amendments

Claim 20 has been amended to specify that the immunostimulatory dinucleotide is not CpG, and to remove the proviso.

Rejection of Claims 20-21 under 35 U.S.C. §103(a): Chaix and Scwartz

Claims 20-21 are rejected as being obvious over Chaix et al and Schwartz. Schwartz is relied upon as disclosing immunostimulatory oligonucleotide sequences comprising a CpG dinucleotide wherein the cytosine is modified. Chaix is relied upon as teaching oligonucleotides comprising a 3'-3' linker and two accessible 5' ends. The asserted motivation to combine the references is that Chaix teaches that the 3'-3' linkage results in a marked increase in oligonucleotide stability, thus one would be motivated to incorporate the 3'-3' linkage of Chaix into the immunostimulatory oligonucleotide of Schwartz to stabilize the oligonucleotide against nucleolytic degradation. It is asserted that there would be a reasonable expectation of success because "the success is well described in the prior art by both references and the underlying techniques are widely used". (Office Action at page 3) Applicants traverse this latter assertion.

One statement in this rejection deserves particular attention and clarification. At page 3 of the Office Action, it is stated that "Of note, Chaix et al teach that there is a marked increase in the structural integrity of an oligonucleotide by inserting a 3'-3' linker and this insertion would have been obvious for any oligonucleotide of any function." This statement critically overstates the teaching of Chaix. Nowhere, does Chaix teach that "this insertion would have been obvious for any oligonucleotide of any function." This is merely an unsupported assertion by the PTO. Clarification of this point is respectfully requested. Nor does Chaix teach that its oligonucleotides have two accessible 5' ends.

Applicants respectfully submit that these errors in the interpretation of Chaix are fatal to the presently maintained rejection.

Chaix relates to the antisense art. It was known in that art that antisense oligonucleotides act by Watson-Crick base pairing to target RNA. Thus, there was no reason to expect that the introduction of a 3'-3' linkage would have any deleterious effect on antisense activity, as such modification would not be expected to affect Watson-Crick base pairing.

In contrast, the rejected claims are drawn to oligonucleotide based immunostimulatory compounds. The mechanism of action of these compounds was not as well understood as the mechanism of action of antisense oligonucleotides. Applicants point out that Chaix does not teach two accessible 5' ends, because the concept of accessible 5' ends and their critical importance was not known at the time the instant application was filed. Nor was it known that accessible 3' ends were not required. Only Applicants specification establishes this. The assertion that "the underlying techniques are widely used" applied only to the antisense art at the time the present application was filed. Thus one skilled in the art of oligonucleotide based immunostimulatory compounds would not have had a reasonable expectation of success in incorporating the 3'-3' linkage of Chaix into the immunostimulatory oligonucleotides of Schwartz, because there was no way to predict that accessibility of 3' ends was not critical to immunostimulatory activity. It could just as well have been that accessible 3' ends were critical and accessible 5' ends were not, based on the knowledge in the art at the time the instant application was filed.

For this reason, Applicants respectfully submit that the combination of Schwartz and Chaix was not obvious in the oligonucleotide based immunostimulatory compound art at the time the present application was filed. Withdrawal of this rejection is respectfully requested.

Rejection of Claims 20, 21 and 41 under 35 U.S.C. §103(a): Chaix, Scwartz, Smee and Schneider and Chait

Claims 20, 21 and 41 are rejected as being obvious over Chaix, Scwartz, Smee and Schneider and Chait. Applicants respectfully submit that this rejection also fails for the reasons discussed above. Neither Smee, nor Schneider and Chait cure the deficiencies of combining Chaix and Schwartz. For this reason, Applicants respectfully request that this rejection be withdrawn.

However, Applicants wish to further address the teachings of Smee and of Schneider and Chait.

Smee is relied upon as teaching that "7-deazaguanosine is immunoenhancing and leads to the induction of interferon in mice." (Office Action at page 11) It is asserted that there would have been a reasonable expectation of success in substituting 7-deazaguanosine for guanosine in the immunostimulatory dinucleotide of Schwartz "given that the underlying techniques are

widely known and commonly used." *Id.* Once again, the relevant art is being confused in this assertion. Smee deals with the nucleoside analog art. There is no suggestion that 7-deazaguanosine, acting as a nucleoside analog bears any similarity in its mode of action to the CpG dinucleotide in oligonucleotide based immunostimulatory compounds. There is simply nothing in Smee (or any other cited reference) to suggest that the substitution of 7-deazaG for G in a Cpg dinucleotide of an oligonucleotide based immunostimulatory compound would result in an active compound.

Schneider and Chait is relied upon as providing the motivation to incorporate 7-deazaG into Schwartz's oligonucleotide based immunostimulatory compound "to increase the stability of CpG-containing oligonucleotides." *Id.* Again, the relevant art is being confused. Schneider and Chait relates to the art of matrix-assisted laser desorption mass spectrometry (MALDI-MS). This reference teaches increased stability of oligonucleotides containing 7-deazaG solely under conditions of MALDI-MS. In the relevant art of oligonucleotide based immunostimulatory compounds, it is physiological stability that is important. Whether such oligonucleotide based immunostimulatory compounds are more stable under conditions of MALDI-MS is entirely irrelevant to their function. Thus, Schneider and Chait could not possibly motivate one skilled in the relevant art to substitute 7-deazaG for guanosine into Schneider's oligonucleotide based immunostimulatory compound. Nor does it provide any suggestion that any such substituted compound would retain immunostimulatory activity.

For these reasons, Applicants respectfully submit that claims 20, 21 and 41 are nonobvious and patentable over this combination of references and request that this rejection be withdrawn.

Double Patenting

Claims 20-21 and 39-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over various claims of co-pending U.S. Application Nos. 11/174,448; 11/234,074; 11/234,075; 11/174,002; 11/173,983; 11/173,794; 11/174,282; 11/173,938; 11/174,450; and 10/757,345.

As stated by the Examiner, this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Please note that U.S.

Application Nos. 11/174,448; 11/234,074; 11/234,075; 11/174,002; 11/173,983; 11/173,794; 11/174,282; 11/173,938; 11/174,450 and 10/757,345 are the later filed applications.

Therefore, if this provisional double patenting rejection is the only remaining rejection in the application, Applicants request that the Examiner withdraw the rejection in the instant [earlier filed] application thereby permitting this application to issue without need of a terminal disclaimer. (See MPEP §804(I)(B)). Applicants will then consider filing a Terminal Disclaimer or take any other action deemed necessary in the later filed, co-pending application.

Claims 20-21 and 39-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over various claims of co-pending U.S. Application No. 10/279,684 (now US Patent 7,276,489).

Please note that U.S. Application No. 10/279,684 is the later filed application. Therefore, if this double patenting rejection is the only remaining rejection in the application, Applicants request that the Examiner withdraw the rejection in the instant [earlier filed] application thereby permitting this application to issue without need of a terminal disclaimer. (See MPEP §804(I)(B)).

Claims 20-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over various claims of co-pending U.S. Application No. 11/270,805.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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